American Journal of Epidemiology

Vol. 176, No. 8
DOI: 10.1093/aje/kws149
Advance Access publication:
October 3, 2012

Original Contribution

Insulin Resistance and the Risk of Stroke and Stroke Subtypes in the Nondiabetic Elderly

Renske G. Wieberdink, Peter J. Koudstaal, Albert Hofman, Jacqueline C. M. Witteman, Monique M. B. Breteler, and M. Arfan Ikram*

* Correspondence to Dr. M. Arfan Ikram, Department of Epidemiology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands (e-mail: m.a.ikram@erasmusmc.nl).

Initially submitted November 8, 2011; accepted for publication February 21, 2012.

Insulin resistance, which plays a key role in the development of diabetes mellitus, is a putative modifiable risk factor for stroke. The aim of this study was to investigate if markers of insulin resistance were associated with risk of stroke in the general elderly population. This study was part of the large population-based Rotterdam Study and included 5,234 participants who were aged 55 years or older and stroke free and diabetes free at baseline (1997–2001). Fasting insulin levels and homeostasis model assessment for insulin resistance were used as markers for insulin resistance. Cox regression was used to determine associations between insulin resistance markers and stroke risk, adjusted for age, sex, and potential confounders. During 42,806 person-years of follow-up (median: 8.6 years), 366 first-ever strokes occurred, of which 225 were cerebral infarctions, 42 were intracerebral hemorrhages, and 99 were unspecified strokes. Fasting insulin levels were not associated with risk of any stroke, cerebral infarction, or intracerebral hemorrhage. Homeostasis model assessment for insulin resistance, which almost perfectly correlated with fasting insulin levels, was also not associated with risk of stroke or stroke subtypes. In conclusion, in this population-based cohort study among nondiabetic elderly, insulin resistance markers were not associated with risk of stroke or any of its subtypes.

cerebral infarction; cohort studies; diabetes mellitus; insulin resistance; intracerebral hemorrhage; stroke

Abbreviations: HOMA-IR, homeostasis model assessment for insulin resistance; ln, natural log.

Type 2 diabetes mellitus is a major risk factor for vascular disease, including stroke (1). Moreover, several studies suggest that precursor stages of diabetes, such as impaired fasting glucose and insulin resistance, already increase the risk of vascular complications (2, 3). However, results from studies investigating coronary heart disease or vascular disease either separately or as a composite endpoint may not apply to stroke. For example, in a large meta-analysis, fasting glucose levels below the threshold for diabetes (7.0 mmol/L) were associated with risk of coronary heart disease but not with risk of stroke (4). The relation between insulin resistance and stroke risk has been studied less extensively.

The "gold standard" for quantifying insulin resistance is the euglycemic hyperinsulinemic glucose clamp technique (5). Because this method is complicated and impractical for epidemiologic research, epidemiologic studies use either the homeostasis model assessment for insulin resistance (HOMA-IR) index or fasting insulin levels as surrogate markers for the degree of insulin resistance. Both markers correlate well with the clamp method (6, 7).

Previous studies have investigated the association between insulin resistance and stroke, but results remain inconclusive. An overview of population-based cohort studies reporting on the association of the HOMA-IR index and fasting insulin levels with risk of stroke in people without diabetes mellitus is given in Tables 1 and 2 (8–14).

Taken together, these studies do not enable us to draw firm conclusions regarding the association between insulin resistance and risk of stroke. Apart from conflicting results,

Table 1. Overview of Prospective Cohort Studies Reporting on the Association Between Fasting Insulin Levels and Risk of Stroke in People Without Diabetes

First Author, Year (Reference No.)	Location	Age Range, years	Women, %	No. at Risk	Follow-up, years			Outcome	No.	Continuous	HR	95% CI	Categorical	HR	95% CI	Covariates
					Mean	Median	Maximum									
Pyorala, 1998 (12)	Finland	34–64	0	970		22.3		Any stroke	70	Per SD	1.07	0.81, 1.41	Quintile 5 vs. Quintiles 1–4	1.54	0.90, 2.62	Age, SBP, smoking, scapular skinfold
Lakka, 2000 (8)	Finland	42–60	0	1,521	9.4			Any stroke	48	Per pmol/L	1.01	1.00, 1.01	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.0 1.5 1.1 1.4	Referent 0.5, 4.0 0.4, 3.0 0.5, 4.0	Age, year, SBP, DBP, smoking, lipids, BMI, WHR, alcohol, white blood cell count, fibrinogen, VO_2 max
Lindahl, 2000 (10)	Sweden	25–64	37	272			12	Any stroke	94				Tertile 1 Tertile 2 Tertile 3	1.0 1.1 2.0	Referent 0.6, 2.3 1.0, 4.0	None
Lawlor, 2007 (9)	United Kingdom	60–79	100	3,246		4.6		Any stroke	52	ln/SD	1.16	0.83, 1.59				Age, SBP, smoking, lipids, BMI, WHR, exercise, SES
Nakamura, 2010 (11)	Japan	35–59	0	2,548	10			Cerebral infarction	13	ln/SD	1.62	1.03, 2.57	Quartile 4 vs. Quartile 1	4.01	1.10, 14.67	Age, SBP, blood pressure-lowering medications, smoking, lipids, waist circumference, alcohol, exercise, lipid-lowering medications
Rasmussen-Torvik, 2010 (13)	United States	45–64	57	12,323			16–18	Cerebral infarction	445				Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	1.00 0.89 1.11 1.10 1.28	Referent 0.63, 1.25 0.82, 1.51 0.80, 1.53 0.92, 1.78	Age, sex, race, center, SBP, blood pressure-lowering medications, smoking, BMI, left ventricular hypertrophy

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; ln, natural log; SBP, systolic blood pressure; SD, standard deviation; SES, socioeconomic status; VO_2 max, peak oxygen uptake; WHR, waist/hip ratio.

Table 2. Overview of Prospective Cohort Studies Reporting on the Association Between the HOMA-IR Index and the Risk of Stroke in People Without Diabetes

First Author, Year (Reference No.)	Location	Age Range, years	Women, %	No. at Risk	Mean Follow-up, years	Outcome	No.	Continuous	HR	95% CI	Categorical	HR	95% CI	Covariates
Tanne, 2009 (22)	Israel	45–74	9	2,938	6.2	Any stroke	172	ln/unit	1.07	0.90, 1.26	Tertile 1 Tertile 2 Tertile 3	1.00 1.07 1.11	Referent 0.72, 1.58 0.74, 1.67	Age, sex, study arm, hypertension, smoking, lipids, BMI, coronary heart disease
Nakamura, 2010 (11)	Japan	35–59	0	2,548	10	Cerebral infarction	13	ln/SD	1.59	1.00, 2.54	Quartile 1 Quartile 2 Quartile 3 Quartile 4	1.00 1.40[a] 1.15[a] 3.23	Referent NS NS 20.82, 12.89	Age, SBP, blood pressure-lowering medications, lipids, waist circumference, alcohol, smoking, exercise, lipid-lowering medications
Rundek, 2010 (14)	United States	68	64	1,509	8.5	Cerebral infarction	46	Per SD[b]	1.04	0.90, 1.19	Quartile 1 Quartile 2[b] Quartile 3[b] Quartile 4[b]	1.00 1.88 0.93 3.11	Referent 0.72, 4.87 0.29, 2.95 1.25, 7.76	Age, sex, race, SBP, DBP, smoking, lipids, waist circumference, alcohol, exercise, education

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment for insulin resistance; HR, hazard ratio; ln, natural log; NS, not significant; SBP, systolic blood pressure; SD, standard deviation.

[a] Hazard ratios and 95% confidence intervals are plotted on a log scale; values not reported.

[b] Adjusted for age only.

most studies were based on relatively small numbers of events and included middle-aged but not elderly people, whereas elderly people are at the highest risk of stroke. Furthermore, all studies focused on any stroke or the subtype cerebral infarction. The association between insulin resistance markers and risk of intracerebral hemorrhage has yet not been investigated.

The aim of the present study was to investigate in a large population-based cohort study among elderly people without diabetes mellitus if the HOMA-IR index and fasting insulin levels were associated with risk of cerebral infarction and intracerebral hemorrhage.

MATERIALS AND METHODS

Source population

The present study was part of the Rotterdam Study, an ongoing prospective population-based cohort study that focuses on causes and consequences of diseases that are frequent in the elderly. The rationale and design of the study have been described extensively elsewhere (15). In 1990, all inhabitants of a well-defined district of the city of Rotterdam in the Netherlands who were aged 55 years or older were invited to participate, and 7,983 persons (of 10,215 invitees) agreed. In the year 2000, the cohort was expanded with 3,011 persons (of 4,472 invitees) who had reached the age of 55 or had moved into the district since the start of the study. There were no additional exclusion criteria; people who were demented or living in a nursing home were invited as well. All participants underwent a comprehensive set of baseline examinations that were repeated during regular follow-up visits. The study was approved by an internal review board, and all participants gave written informed consent to participate in the study.

Measurement of serum glucose and insulin levels and HOMA-IR

Venous blood samples were taken at the research center after an overnight fast and stored at −80°C in a number of 5-mL aliquots. Serum glucose levels were determined by using the glucose hexokinase method within 1 week after sampling (16). Serum insulin levels were determined in samples that had been kept frozen from baseline (1997–2001) until usage in 2008 and were measured on a Roche Modular Analytics E170 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) by electrochemiluminescence immunoassay technology. This assay does not cross-react with proinsulin or C-peptide. The intraassay repeatability of our assay showed a coefficient of variation of 1.0%. The day-to-day variation of the assay (i.e., intermediate precision) yielded a coefficient of variation of 3.6%. These numbers indicate excellent reliability of the insulin assay in our study. The following formula was used to calculate HOMA-IR: [fasting insulin (mU/L) × fasting glucose (mmol/L)] / 22.5 (7).

Definition of diabetes mellitus

Diabetes mellitus was defined as a fasting serum glucose level of ≥7.0 mmol/L and/or the use of blood glucose-lowering drugs.

Assessment of stroke

Stroke was defined according to World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin (17). History of stroke at baseline was assessed during the baseline interview and verified by review of medical records. After enrollment, participants were continuously monitored for incident stroke by use of the following strategies. General practitioners are the gatekeepers of our health-care system; they collect and register all medical events and hospital visits occurring from birth to death. Our study participants were all aligned to a general practitioner. Moreover, our study database was electronically coupled to the general practitioners' databases, continuously monitoring medical records for reported stroke events. Furthermore, at regular intervals, well-trained research assistants visited these general practitioners. Nursing home physicians' files and files from general practitioners of participants who moved out of the district were checked on a regular basis as well. Additional information was obtained from hospital records. The records were screened for the occurrence of stroke events or stroke-like symptoms. If stroke-like events or stroke-like symptoms were found, the information was collected, reviewed by a research physician, and verified by an experienced stroke neurologist. If a stroke was diagnosed, it was further classified as cerebral infarction or intracerebral hemorrhage on the basis of neuroimaging reports. If neuroimaging was lacking, a stroke was classified as unspecified. Subarachnoid hemorrhages were not considered stroke events.

Participants were followed from study entry to stroke, death, last health status update when they were known to be stroke free, or January 1, 2009, whichever came first. At study closeout, the stroke status was unknown for 17% of participants. If the date "last known to be stroke free" was earlier than January 1, 2009, the follow-up time was censored at that particular date. These participants contributed person-years only until the day they were last known to be stroke free. Completeness of follow-up, calculated by dividing the sum of observed person-years by the sum of potential person-years × 100%, was 97.6% (18).

Other measurements

Trained research physicians visited all participants at home for standardized questionnaires about their health status and medical history, including questions about current medication use and cigarette smoking behavior. Subsequently, all participants visited the research center twice for physical examination and blood sampling. Blood pressure was calculated as the average of 2 measurements

at the right brachial artery with a random-zero sphygmomanometer after 5 minutes of rest while the subject was in a sitting position. Hypertension was defined as a diastolic blood pressure of ≥90 mm Hg and/or a systolic blood pressure of ≥140 mm Hg, and/or the use of blood pressure-lowering medication (19). Fasting serum total cholesterol, high density lipoprotein cholesterol, and triglyceride levels were measured by using enzymatic colorimetric methods (Hitachi Analyzer; Roche Diagnostics). Von Willebrand factor antigen was determined with an in-house enzyme-linked immunosorbent assay, using polyclonal rabbit anti-human von Willebrand factor antibodies (DakoCytomation, Glostrop, Denmark) for catching and tagging (20). Body mass index was calculated as weight (kg)/height (m)^2. The waist/hip ratio was calculated by dividing the waist circumference (cm) by the hip circumference (cm).

Population for analysis

The present analyses were based on participants of the third survey of the 1990 subcohort ($n = 5,990$) and participants of the first survey of the 2000 subcohort ($n = 3,011$). Of this pooled cohort of 9,001 participants, 8,530 persons were stroke free at baseline and had given written informed consent for the collection of follow-up data from general practitioners. Of these 8,530 persons, we excluded 2,661 persons due to the following reasons: death, refusal, or physical inability ($n = 1,883$); failure of blood draw or storage ($n = 479$); or nonfasting state ($n = 299$). This resulted in 5,869 persons, of whom additionally 635 were excluded for prevalent diabetes. The final population for analysis hence included 5,234 participants.

Statistical analysis

We estimated pairwise Pearson correlation coefficients to determine the strength of the linear relations among fasting glucose levels, fasting insulin levels, and the HOMA-IR index. Insulin levels and the HOMA-IR index were natural log transformed because of nonnormality of their distributions. Cox proportional hazards regression was used to calculate hazard ratios and 95% confidence intervals for the associations between fasting insulin levels, the HOMA-IR index, and fasting glucose levels and the risk of stroke and the stroke subtypes, cerebral infarction and intracerebral hemorrhage. Only first-ever strokes were included in the analyses. Hazard ratios were calculated by analyzing natural log (ln)insulin, (ln)HOMA-IR, and glucose per standard deviation increase. To verify the (log-)linearity of associations, we also categorized the exposure levels in quartiles using the lowest quartile as the reference category. The linear trend across quartiles was tested by including median values of quartile categories as a continuous variable in the model. All analyses were adjusted for age and sex (model 1) and additionally for age, sex, and a propensity score that included the following potential confounders: systolic blood pressure, blood pressure-lowering medication use, serum total cholesterol level, high density lipoprotein cholesterol level, triglyceride level, lipid-lowering medication use, current cigarette smoking, body mass index, waist/hip ratio, and plasma von Willebrand factor level (model 2) (21). The main reason to adjust for a propensity score instead of individual covariates was that the number of intracerebral hemorrhages in our study was small in comparison to the number of potential confounders. Missing values in covariates, which varied from 0.0% to 5.1% per variable, were imputed with a linear regression model based on age and sex. All analyses were performed by using PASW Statistics for Windows, version 17.0 (SPSS, Inc., Chicago, Illinois).

Table 3. Baseline Characteristics of the Study Population ($n = 5,234$), the Rotterdam Study, 1997–2008

Continuous Variables	No.	%	Median	IQR
Age, years			67.9	62.4–74.6
Systolic blood pressure, mm Hg			140	127–155
Diastolic blood pressure, mm Hg			76	69–84
Total cholesterol, mmol/L			5.8	5.2–6.5
HDL cholesterol, mmol/L			1.4	1.1–1.6
Triglycerides, mmol/L			1.3	1.0–1.8
Body mass index[a]			26.3	24.1–28.9
Waist/hip ratio, cm/cm			0.92	0.84–0.98
Von Willebrand factor, IU/mL			1.2	0.9–1.6
Glucose, mmol/L			5.5	5.2–5.9
Insulin, pmol/L			65	46–91
HOMA-IR index			2.3	1.6–3.3
Female sex	3,017	57.6		
Current cigarette smoking	908	17.5		
Blood pressure-lowering medication	1,599	32.2		
Hypertension	3,337	65.3		
Lipid-lowering medication	592	11.9		

Abbreviations: HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; IQR, interquartile range.

[a] Body mass index: weight (kg)/height (m)^2.

RESULTS

Baseline characteristics of the study population are shown in Table 3. The median age was 67.9 years, and 57.6% were women. The pairwise Pearson correlation coefficient for (ln)insulin and (ln)HOMA-IR was 0.99, indicating almost perfect linearity. Glucose and (ln)HOMA-IR were only weakly correlated ($r = 0.51$), as were glucose and (ln)insulin ($r = 0.37$).

During 42,806 person-years of follow-up (median: 8.6 years), 366 participants developed a first-ever stroke, which was classified in 225 as cerebral infarction, in 42 as

Table 4. Associations of Insulin, HOMA-IR, and Glucose With Risk of Any Stroke, the Rotterdam Study, 1997–2008

	At Risk		No. of Events	Model 1[a]		Model 2[b]	
	No.	Person-Years		HR	95% CI	HR	95% CI
Insulin level, pmol/L							
Per SD[c]	5,234	42,806	366	0.94	0.85, 1.05	0.86	0.76, 0.98
Quartile 1 (10–46)	1,318	10,747	94	1.00	Referent	1.00	Referent
Quartile 2 (47–64)	1,269	10,425	91	0.96	0.72, 1.28	0.91	0.68, 1.22
Quartile 3 (65–90)	1,338	11,038	94	0.98	0.74, 1.30	0.88	0.65, 1.19
Quartile 4 (91–430)	1,309	10,595	87	0.95	0.71, 1.27	0.80	0.57, 1.12
P_{trend}				0.76		0.21	
HOMA-IR							
Per SD[c]	5,234	42,806	366	0.95	0.86, 1.06	0.86	0.76, 0.98
Quartile 1 (0.3–<1.6)	1,310	10,638	100	1.00	Referent	1.00	Referent
Quartile 2 (1.6–<2.3)	1,303	10,848	84	0.78	0.58, 1.04	0.73	0.54, 0.97
Quartile 3 (2.3–<3.3)	1,313	10,727	96	0.96	0.73, 1.28	0.84	0.62, 1.13
Quartile 4 (3.3–15.2)	1,308	10,592	86	0.86	0.64, 1.14	0.68	0.49, 0.96
P_{trend}				0.59		0.08	
Glucose level, mmol/L							
Per SD	5,234	42,806	366	1.05	0.94, 1.16	1.00	0.90, 1.11
Quartile 1 (3.7–<5.2)	1,221	10,069	91	1.00	Referent	1.00	Referent
Quartile 2 (5.2–<5.5)	1,555	12,783	102	0.89	0.67, 1.18	0.86	0.65, 1.14
Quartile 3 (5.5–<5.9)	1,031	8,415	61	0.78	0.57, 1.08	0.73	0.52, 1.01
Quartile 4 (5.9–6.9)	1,427	11,539	112	1.06	0.80, 1.40	0.94	0.70, 1.26
P_{trend}				0.69		0.65	

Abbreviations: CI, confidence interval; HR, hazard ratio; HOMA-IR, homeostasis model assessment for insulin resistance; SD, standard deviation.

[a] Model 1: adjusted for age and sex.

[b] Model 2: adjusted for age, sex, and a propensity score (current smoking, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, high density lipoprotein cholesterol, triglycerides, lipid-lowering medication use, von Willebrand factor, body mass index, and waist/hip ratio).

[c] Insulin levels and the HOMA-IR index are natural log transformed.

intracerebral hemorrhage, and in 99 as unspecified. Table 4 shows the associations between the HOMA-IR index, fasting insulin levels, and fasting glucose levels and risk of any stroke. The HOMA-IR index and fasting insulin levels were not associated with risk of stroke after adjustment for age and sex (model 1). However, the HOMA-IR index and insulin levels were borderline inversely associated with risk of stroke after adjustment for multiple putative confounders (model 2). Furthermore, the effect estimates for HOMA-IR and insulin levels were practically identical, as could be expected given their high correlation. Fasting glucose levels in the nondiabetic range were also not associated with risk of stroke. However, because the pattern across glucose quartiles seemed suggestive of a curvilinear relation, we additionally performed a quadratic trend test, which did not reach statistical significance at the conventional $\alpha = 0.05$ level ($P = 0.08$).

Associations between insulin levels, the HOMA-IR index, and glucose levels and the risk of stroke subtypes, cerebral infarction and intracerebral hemorrhage, are shown in Table 5. HOMA-IR and fasting insulin levels were not associated with cerebral infarction after adjustment for age and sex, but they were inversely associated with cerebral infarction after adjustment for multiple confounders, similar to what we found for any stroke. Fasting glucose levels were not associated with risk of cerebral infarction in either model. Table 5 further shows that neither fasting insulin levels, nor HOMA-IR, nor fasting glucose levels were associated with risk of intracerebral hemorrhage.

Because we did not observe any association between increasing glucose or insulin levels and stroke, we checked in a post-hoc analysis whether diabetes mellitus was associated with risk of stroke in our study cohort. For this purpose, we added the participants with diabetes mellitus at baseline ($n = 635$), whom we had excluded for the other analyses, to the population for analysis, and we used Cox regression to calculate the association between diabetes mellitus and risk of stroke, adjusted for age, sex, and a propensity score of potential confounders (models 1 and 2). Diabetes mellitus was indeed associated with an increased risk of stroke,

Table 5. Associations of Insulin, HOMA-IR, and Glucose With Risk of Cerebral Infarction and Intracerebral Hemorrhage, the Rotterdam Study, 1997–2008

	Model 1[a]		Model 2[b]	
	HR	95% CI	HR	95% CI
Cerebral infarction ($n = 225$)				
Insulin level[c] per SD	0.92	0.81, 1.06	0.83	0.71, 0.98
HOMA-IR index[c] per SD	0.93	0.82, 1.06	0.83	0.71, 0.97
Glucose level per SD	1.02	0.90, 1.17	0.97	0.85, 1.12
Intracerebral hemorrhage ($n = 42$)				
Insulin level[c] per SD	1.00	0.73, 1.35	1.08	0.74, 1.55
HOMA-IR index[c] per SD	1.03	0.76, 1.39	1.11	0.76, 1.60
Glucose level per SD	1.19	0.89, 1.60	1.16	0.85, 1.59

Abbreviations: CI, confidence interval; HOMA-IR, homeostasis model assessment for insulin resistance; HR, hazard ratio; SD, standard deviation.

[a] Model 1: adjusted for age and sex.

[b] Model 2: adjusted for age, sex, and a propensity score (current smoking, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, high density lipoprotein cholesterol, triglycerides, lipid-lowering medication use, von Willebrand factor, body mass index, and waist/hip ratio).

[c] Insulin levels and the HOMA-IR index are natural log transformed.

independent of confounders (hazard ratio = 1.59, 95% confidence interval: 1.06, 2.40).

DISCUSSION

In this prospective population-based cohort study among nondiabetic elderly people, we found no association between insulin resistance markers and risk of stroke or the stroke subtypes, cerebral infarction and intracerebral hemorrhage. We also confirmed previous findings that fasting glucose levels below the diabetes threshold are not associated with risk of stroke or its subtypes.

We excluded diabetic elderly from the study population because we aimed to study fasting insulin levels as a marker of insulin resistance. Whereas fasting insulin levels accurately reflect the degree of insulin resistance in people without diabetes, in people with diabetes mellitus they do not. Moreover, in people with diabetes mellitus, fasting insulin levels may be low because of the combined effects of insulin resistance and impaired insulin secretion.

Previous studies that investigated the association between fasting insulin levels and stroke risk observed either borderline significant associations or positive associations that were strongly attenuated after adjustment for confounders, particularly after adjustment for components of the metabolic syndrome (8–10, 12, 13), though one study reported a positive association that remained after adjustment for confounders (Table 1) (11). However, all studies but one were conducted among middle-aged men and women (8, 10–13). The only study carried out in an older population was restricted to women and found no association (9). Our finding that fasting insulin levels are not associated with risk of stroke in elderly men and women adds to these previous findings and fits with prior knowledge of diabetes mellitus being a stronger risk factor for stroke in younger than in older people (4). The role of insulin resistance in the elderly might be different from its role in middle-aged or young people. We have tried to carefully adjust for confounding factors and cardiovascular risk factors. Nevertheless, we cannot completely rule out the possibility that selective survival and mortality due to competing risks may have influenced our results.

Associations between the HOMA-IR index and stroke risk have also been investigated before (11, 14). Because HOMA-IR was reported to correlate better with the euglycemic hyperinsulinemic glucose clamp technique than fasting insulin levels, recent epidemiologic studies tend to use HOMA-IR as a marker for insulin resistance (6, 7). However, in normoglycemic conditions, fasting insulin levels also accurately reflect insulin resistance (7). Therefore, it was not surprising that we observed an almost perfect correlation between the fasting insulin level and the HOMA-IR index ($r = 0.99$). Nonetheless, for the sake of comparability with other studies, we present results for both the HOMA-IR index and the fasting insulin level. Three follow-up studies addressed the association between HOMA-IR and stroke with conflicting results (Table 2). One study found no association but was conducted in a highly selected study population of people with preexisting coronary heart disease (22). Two other studies, one of which included only 13 events (11) and the other only 46 events (14), reported (borderline) positive associations. However, because the effect estimates for successive HOMA-IR quartiles in these studies were fluctuating, the interpretation of these findings remains questionable. We showed in the largest study so far that HOMA-IR, like fasting insulin level, is not associated with stroke or cerebral infarction. Furthermore, our study shows that, in normoglycemic elderly, HOMA-IR does not provide any additional information beyond that provided by the fasting insulin level.

It should be noted that, though we found null associations between insulin and the HOMA-IR index and stroke in minimally adjusted analyses, we found inverse associations when we adjusted for multiple putative confounders. On the basis of prior knowledge, we consider a protective effect of increasing insulin resistance on stroke risk highly unlikely. Instead, we consider it more likely that the inverse association is a spurious relation introduced after the adjustment for strong confounders.

Because diabetes mellitus is associated with the risks of both thromboembolic vascular disease and intracerebral hemorrhage, we also investigated the relation between insulin resistance markers and intracerebral hemorrhage (4). We found that neither HOMA-IR nor fasting insulin levels were associated with an increased risk. We are not aware of any studies reporting on the association between HOMA-IR or fasting insulin level and risk of intracerebral

hemorrhage. Therefore, our study provides new information that insulin resistance does not play a major role in the occurrence intracerebral hemorrhage. However, because our results were based on only 42 intracerebral hemorrhages, additional studies are needed to confirm these findings.

Diabetes mellitus is diagnosed if the fasting glucose level exceeds 7.0 mmol/L (23). The rationale for this threshold is that the presence of retinopathy lesions increases at higher levels (23). The observation that diabetes mellitus and glucose levels above 7.0 mmol/L associate with stroke risk, whereas precursor stages of diabetes do not, indicates that a similar threshold may hold for stroke risk (4). Besides, because the retinal microvasculature and the cerebral microvasculature have many characteristics in common (24), it is not surprising that the deleterious effects of hyperglycemia, hyperinsulinemia, and insulin resistance start at similar thresholds in both retinopathy and stroke.

We studied 2 markers of insulin resistance that are traditionally considered to reliably reflect the degree of insulin resistance in people without diabetes mellitus, that is, fasting insulin level and HOMA-IR. However, we note that investigating postprandial insulin measurements and thus postprandial insulin resistance would have been of additional value, particularly because postprandial insulin measurements were recently shown to associate with risk of stroke in elderly persons (25). Unfortunately, in the present study population, we did not have postprandial insulin measurements. We have shown that fasting markers of insulin resistance do not associate with stroke risk. Future studies should further explore whether postprandial characteristics of insulin resistance are better markers of stroke risk than fasting characteristics.

Strengths of the study include the prospective and population-based design, the large number of participants, and the long duration and completeness of the follow-up. However, this study also has some limitations. We did not include 2,477 participants in the analysis because of incomplete data on fasting glucose levels or fasting insulin levels. These participants were older (median age: 74.5 vs. 67.9 years) and more often female (68% vs. 58%) in comparison to the study population. Therefore, it is possible that exclusion of these participants resulted in some selection bias. However, in longitudinal studies, a more important source of selection bias is loss to follow-up, which was only 2.4% in this study. Another consideration is that, inherent to the population-based design and rigorous stroke monitoring procedure, neuroimaging had not been performed in all stroke cases. As a result, 27% of the strokes could not be classified as either cerebral infarction or intracerebral hemorrhage. However, because the association between fasting insulin levels and unspecified stroke risk (per standard deviation = 0.86, 95% CI: 0.68, 1.08 (Model 2)) was not materially different from the association between insulin levels and cerebral infarction or intracerebral hemorrhage (Table 4), we consider this misclassification of limited importance. In addition, fasting insulin levels were measured only once, so we could not investigate whether results were influenced by intraindividual fluctuations in insulin resistance.

To conclude, in this population-based cohort study among nondiabetic elderly people, we found no evidence for an association between markers of insulin resistance and risk of any stroke, cerebral infarction, or intracerebral hemorrhage. Taken together with previous findings that fasting glucose levels below the diabetes threshold are not associated with stroke risk (4), these results indicate that, in contrast with overt diabetes mellitus, precursor stages of diabetes mellitus, as measured by fasting glucose levels, fasting insulin levels, and the HOMA-IR index, do not seem to be important risk factors for stroke, cerebral infarction, or intracerebral hemorrhage.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands (Renske G. Wieberdink, Albert Hofman, Jacqueline C. M. Witteman, Monique M. B. Breteler, M. Arfan Ikram); Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands (Renske G. Wieberdink, Peter J. Koudstaal); Department of Radiology, Erasmus University Medical Center, Rotterdam, the Netherlands (M. Arfan Ikram); and German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (Monique M. B. Breteler).

The Rotterdam Study is supported by the Erasmus Medical Center Rotterdam; the Erasmus University Rotterdam; the Netherlands Organization for Scientific Research (NWO); the Netherlands Organization for Health Research and Development (ZonMW); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture, and Science; the Ministry of Health, Welfare, and Sports; the European Commission (DG XII); and the Municipality of Rotterdam.

The funding sources had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Conflict of interest: none declared.

REFERENCES

1. Creager MA, Lüscher TF, Cosentino F, et al. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Circulation*. 2003;108(12):1527–1532.
2. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol*. 2010;55(13):1310–1317.
3. Ruige JB, Assendelft WJ, Dekker JM, et al. Insulin and risk of cardiovascular disease: a meta-analysis. *Circulation*. 1998;97(10):996–1001.
4. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Emerging Risk Factors Collaboration. *Lancet*. 2010;375(9733):2215–2222.

5. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;237(3):E214–E223.
6. Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol*. 1993;137(9): 959–965.
7. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419.
8. Lakka HM, Lakka TA, Tuomilehto J, et al. Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Arch Intern Med*. 2000;160(8): 1160–1168.
9. Lawlor DA, Fraser A, Ebrahim S, et al. Independent associations of fasting insulin, glucose, and glycated haemoglobin with stroke and coronary heart disease in older women. *PLoS Med*. 2007;4(8):e263. (doi:10.1371/journal.pmed.0040263).
10. Lindahl B, Dinesen B, Eliasson M, et al. High proinsulin levels precede first-ever stroke in a nondiabetic population. *Stroke*. 2000;31(12):2936–2941.
11. Nakamura K, Sakurai M, Miura K, et al. Homeostasis model assessment of insulin resistance and the risk of cardiovascular events in middle-aged non-diabetic Japanese men. *Diabetologia*. 2010;53(9):1894–1902.
12. Pyörälä M, Miettinen H, Laakso M, et al. Hyperinsulinemia and the risk of stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Stroke*. 1998;29(9):1860–1866.
13. Rasmussen-Torvik LJ, Yatsuya H, Selvin E, et al. Demographic and cardiovascular risk factors modify association of fasting insulin with incident coronary heart disease and ischemic stroke (from the Atherosclerosis Risk In Communities Study). *Am J Cardiol*. 2010;105(10): 1420–1425.
14. Rundek T, Gardener H, Xu Q, et al. Insulin resistance and risk of ischemic stroke among nondiabetic individuals from the northern Manhattan study. *Arch Neurol*. 2010;67(10): 1195–1200.
15. Hofman A, van Duijn CM, Franco OH, et al. The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol*. 2011;26(8):657–686.
16. Neeley WE. Simple automated determination of serum or plasma glucose by a hexokinase-glucose-6-phosphate dehydrogenase method. *Clin Chem*. 1972;18(6):509–515.
17. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ*. 1976;54(5): 541–553.
18. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet*. 2002;359(9314): 1309–1310.
19. 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. Guidelines Subcommittee. *J Hypertens*. 1999;17(2):151–183.
20. Wieberdink RG, van Schie MC, Koudstaal PJ, et al. High von Willebrand factor levels increase the risk of stroke: the Rotterdam Study. *Stroke*. 2010;41(10):2151–2156.
21. D'Agostino RB Jr. Propensity scores in cardiovascular research. *Circulation*. 2007;115(17):2340–2343.
22. Tanne D, Tenenbaum A, Boyko V, et al. Increased insulin resistance and risk of incident cerebrovascular events in patients with pre-existing atherothrombotic disease. *Eur J Neurol*. 2009;16(11):1217–1223.
23. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2011;34(suppl 1): S62–S69.
24. Wong TY. Is retinal photography useful in the measurement of stroke risk? *Lancet Neurol*. 2004;3(3):179–183.
25. Thacker EL, Psaty BM, McKnight B, et al. Fasting and post-glucose load measures of insulin resistance and risk of ischemic stroke in older adults. *Stroke*. 2011;42(12): 3347–3351.